



Short Communication

A Green Method for Preparing Thioctic Acid Hydrogel at Room Temperature

Xiaoxia Wang¹, Jiamin Qin¹, Yanna Lv^{1*}, Jinlong Ma^{1,2,3*}

¹School of Pharmacy, Weifang Medical University, Weifang, Shandong Province, China

²Collaborative Innovation Center for Target Drug Delivery System, Weifang Medical University, Weifang, Shandong Province, China

³Shandong Engineering Research Center for Smart Materials and Regenerative Medicine, Weifang Medical University, Weifang, Shandong Province, China

*Correspondence to: Yanna Lv, PhD, Associate Professor, School of Pharmacy, Weifang Medical University, 4948 Shengli East Street, Weifang 261053, China; Email: lynlyna@163.com;

Jinlong Ma, PhD, Research Fellow, School of Pharmacy, Weifang Medical University, 4948 Shengli East Street, Weifang 261053, China; Email: majinlong99@hotmail.com

Received: March 14, 2022 Accepted: April 8, 2022 Published: May 23, 2022

Abstract

Objective: Although thioctic acid (TA) hydrogel is produced via thioctic acid ring-opening polymerization, the reaction temperature was at thioctic acid melting temperature (70°C), which is energy inefficient. The principal objective of the present study was to synthesize TA hydrogels at room temperature.

Methods: Temperature was used as a variable to prepare TA hydrogel, and the feasibility of synthesis method was verified.

Results: Tannic acid-TA hydrogel was synthesized at room temperature using tannic acid as cross-linking agent. Furthermore, the AuTA hydrogel was also synthesized at room temperature using gold nanostars as cross-linking agent.

Conclusion: TA hydrogels were synthesized at room temperature, and its reaction mechanism was preliminarily speculated. Our finding contributes to a much greener supramolecular hydrogel, particularly in the age of the energy crisis.

Keywords: hydrogel, thioctic acid, tannic acid, room temperature

Citation: Wang X, Qin J, Lv Y, Ma J. A Green Method for Preparing Thioctic Acid Hydrogel at Room Temperature. *J Mod Polym Chem Mater*, 2022; 1(2): 8. DOI: 10.53964/jmpcm.2022008.

1 INTRODUCTION

Recently, a small molecule of biological origin known as thioctic acid formed an amorphous supramolecular network

by taking advantage of its disulfide-containing main chain cross-linked by hydrogen bonds and metal carbonyl complexes^[1-4]. However, this supramolecular network is not

the hydrogel due to the poor water solubility of thioctic acid, in spite of the similarity to hydrogels. Chen et al.^[5] innovated the synthesis of the tannic acid-thioctic acid (TATA) hydrogel by tannic acid and thioctic acid at the melting temperature of the latter in an aqueous solution (70°C) without any toxic organic crosslinkers or heavy metal ions.

Due to dynamic disulfide exchange, the five-membered ring-containing disulfide link undergo thermal-initiated ring-opening polymerization (ROP) as a fluid liquid at a melting temperature of 70°C, creating the main linear covalent backbone. After cooling, the linear polymer is effectively cross-linked by carboxylic side chains dimerized by H-bonds, resulting in a clear solid polymer^[6] (Figure 1A). To solve the difficulty of poly (TA) metastability, the authors employed tannic acid, a naturally occurring chemical, to quench the terminal diradicals of poly (TA) via a polyphenol-thiyl radical nucleophilic addition reaction, therefore strengthening the network by covalent cross-linking^[5]. It's a genius idea to employ two naturally existing small molecules to synthesize supramolecular hydrogel.

It is well acknowledged that the ROP of thioctic acid happened at the melting temperature (70°C)^[1,5-8]. However, whether 70°C is the temperature from solid to liquid or the reaction temperature remains to be clarified. Zhang et al.^[9] reported that sodium thioctate could assemble into a highly ordered supramolecular layered network in an aqueous solution at room temperature (Figure 1B and Figure 1C). Wang et al.^[3] discovered that α -thioctic acid could realize concentration-induced ROP in ethanol (containing ionic liquid) at ambient conditions (Figure 2). Sodium thioctate could be soluble in the water, and thioctic acid could be dissolved in ethanol (containing ionic liquid) but insoluble in water. With the action of tris base, thioctic acid turns from insoluble into soluble in the water even at a high concentration. Therefore, whether the TA hydrogel by tannic acid and thioctic acid could be synthetic at room temperature at a tris-base solution or not?

2 MATERIALS AND METHODS

2.1 Materials

Thioctic acid, chloroauric acid trihydrate (99%), tannic acid, HEPES, and tris base were purchased from Meryer (Shanghai) Chemical Technology Co., Ltd. All chemicals were used without further purification.

2.2 Methods

2.2.1 Preparation of Gold Nanostars (AuNSs)

Gold nanostar was prepared by HEPES reduction of chloroauric acid trihydrate. 6mL HEPES aqueous solution (100mm, pH7.4) were put into a 20mL glass vial and 100 μ L chloroauric acid trihydrate aqueous solution (10mg/mL) was quickly added into it under vigorous stirring. After mixing evenly (10-30s), let it stand at room temperature (25°C). After about 1h, when the color of the solution gradually changes

from colorless and transparent to dark green, the preparation of gold nanostar is completed and stored in 4 refrigerators.

2.2.2 Preparation of TATA Hydrogels

Typically, 1g tannic acid and 1g tris base were dissolved in 4mL distilled water. The above solution was added to 2g thioctic acid, and the resulting mixture was vortexed for 60s. The obtained TATA copolymer was placed at RT for 0.5-1h and the TATA hydrogel was secured.

2.2.3 Preparation of AuTA Hydrogels

First, tris base (1g) was dissolved in AuNSs solution (4mL). Then thioctic acid (2g) was added to the mixture, and the resulting mixture was vortexed for 60s at RT. The obtained AuTA copolymer was placed at RT for 0.5-1h and the AuTA hydrogel was secured.

3 RESULTS AND DISCUSSION

We hypothesized that thioctic acid tris base solution is identical to sodium thioctate aqueous solution or thioctic acid ethanol solution (containing ionic liquid). To test this hypothesis, we conducted a series of experiments by changing the temperature from 70°C to room temperature. Comparing the reaction at 70°C to room temperature, TATA copolymer obtained at room temperature after vortexed for 60s exhibited more remarkable viscosity than that at 70°C, with insignificant difference in appearance (Figure 3A). Then, we compared the impact of different post-processing, including being frozen at $-20\pm 3^\circ\text{C}$ for 1h and thawed at 25°C for 1h, or just placed at RT for 2h. The appearance comparison showed that the reaction temperature and post-processing have no impact on the TATA hydrogel (Figure 3B). It is worth noting, the TATA hydrogel on the bottom (Figure 3B) was caused in the loading process rather than falling down. According to Zhang's report^[9], the UV-vis characteristic absorption maximum would be blue shifted after the realization of ROP of TA. As observed, the UV-vis reflection spectrum of TATA hydrogel (RT) was the same as TATA hydrogel (70°C) (Figure 3C), and the characteristic absorption maximum of thioctic acid (330nm) disappeared. However, the characteristic absorption maximum of TATA hydrogel (about 312nm) was hardly observed due to tannic acid. The Fourier transform infrared was also used to verify the occurrence of ROP (Figure 3D). This experiment shows that the ROP of thioctic acid took place in solutions instead of 70°C, which is consistent with concentration-induced ROP achieved by the assembly of lipoic acid in ethanol (containing an ionic liquid) and sodium lipoic acid in an aqueous solution at room temperature^[3,9].

To expand the application of the thioctic acid-based hydrogel at RT, we also tested other linkers. Gold nanoparticles could produce a reaction with -SH. Armed with this knowledge, gold nanostars (AuNSs) were chosen as a crosslinker to quench the terminal diradicals of poly (TA). As TATA hydrogel, AuTA hydrogel has good properties

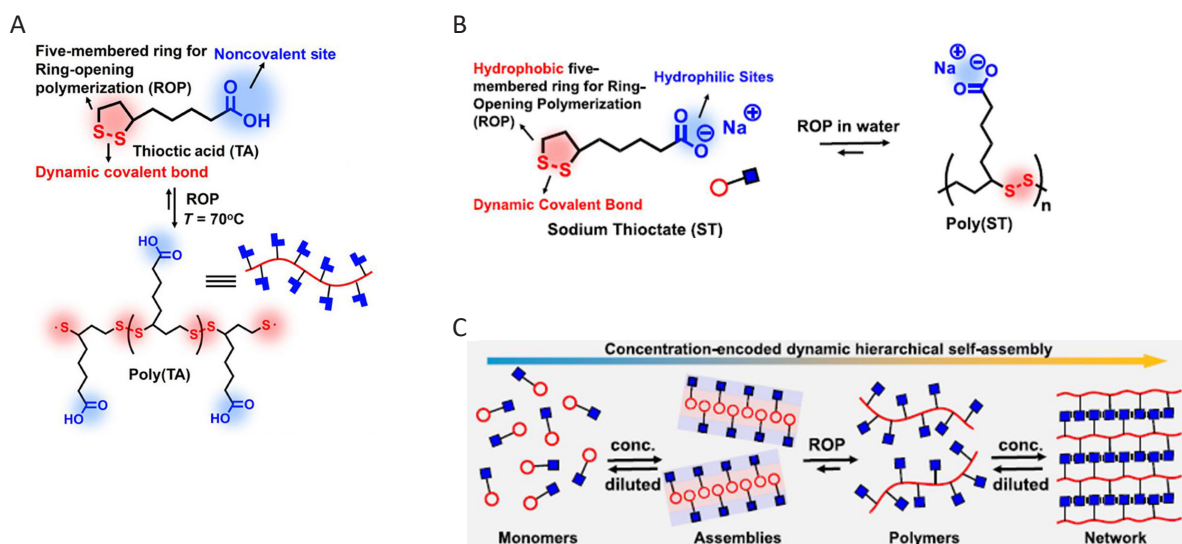


Figure 1. Schematic representation of ROP of thioctic acid. A: Schematic representation of thioctic acid synthesis pathway for the copolymer network. Reprinted from Ref.^[2] with permission. Copyright 2018, Da-Hui Qu; B and C: Self-assembly process of sodium thioctate water solution, Reprinted from Ref.^[3] with permission. Copyright 2019, Da-Hui Qu.

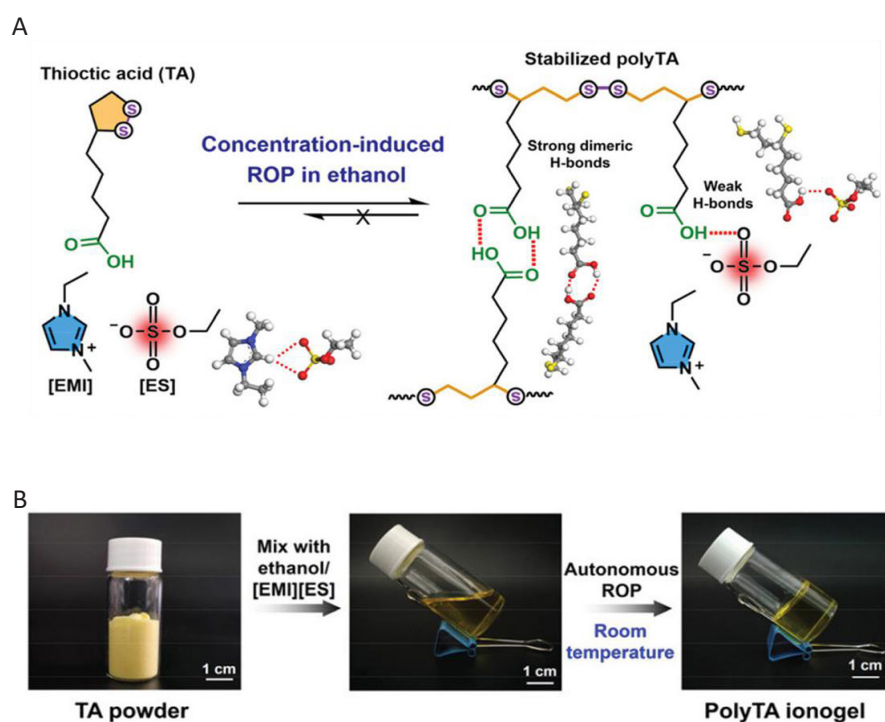


Figure 2. The ROP of thioctic acid in ethanol (containing ionic liquid) at ambient conditions. A: Schematic illustration of concentration-induced ROP of TA in ethanol at room temperature; B: Photos of the rapid ROP of TA mixed with ethanol and [EMI][ES]. Reprinted from Ref.^[7] with permission. Copyright 2021, Wiley-VCH Verlag GmbH & Co. KGaA.

(Figure 4A and Figure 4B), and it was also verified by UV–vis and Fourier transform infrared (Figure 4C and Figure 4D). Unlike TATA hydrogel, the characteristic absorption maximum of AuTA hydrogel can be observed at about 312nm without tannic acid interference.

4 CONCLUSION

In conclusion, we synthesized the TATA hydrogels at room temperature and preliminarily hypothesized the reaction mechanism. Furthermore, we applied the same

method that has synthesized the AuTA hydrogel at room temperature. This is a significant step forward for TA hydrogels in the biomedical field. These findings may aid in the development of green supramolecular hydrogel against global energy dilemma.

Acknowledgments

This work was supported by the Natural Science Foundation of Shandong Province (No. ZR2019BB071) and the Science and Technology Innovation Fund for

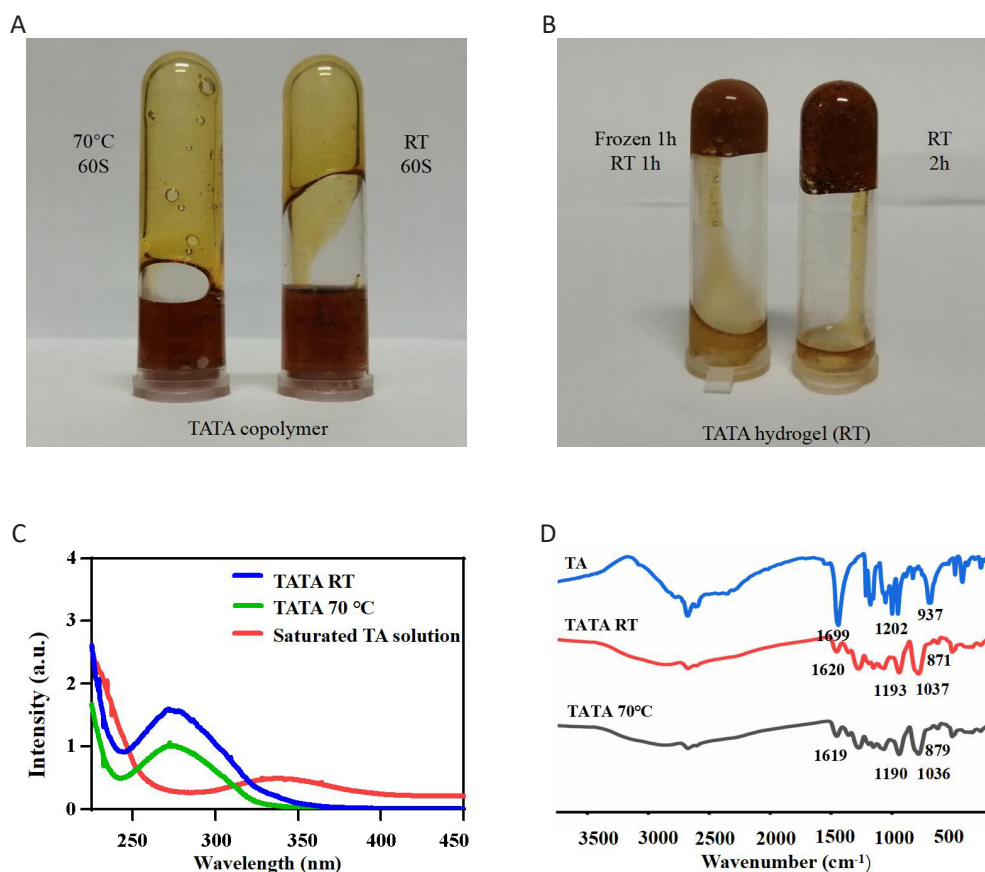


Figure 3. Photographs of TATA copolymer and TATA hydrogel were obtained at different temperatures. A: TATA copolymer synthesized at 70°C (left) and RT (right); B: TATA hydrogel synthesized at RT with different post-processing; C: UV-vis absorption spectra; D: FT-IR spectra of TA and the TATA hydrogel (RT and 70°C).

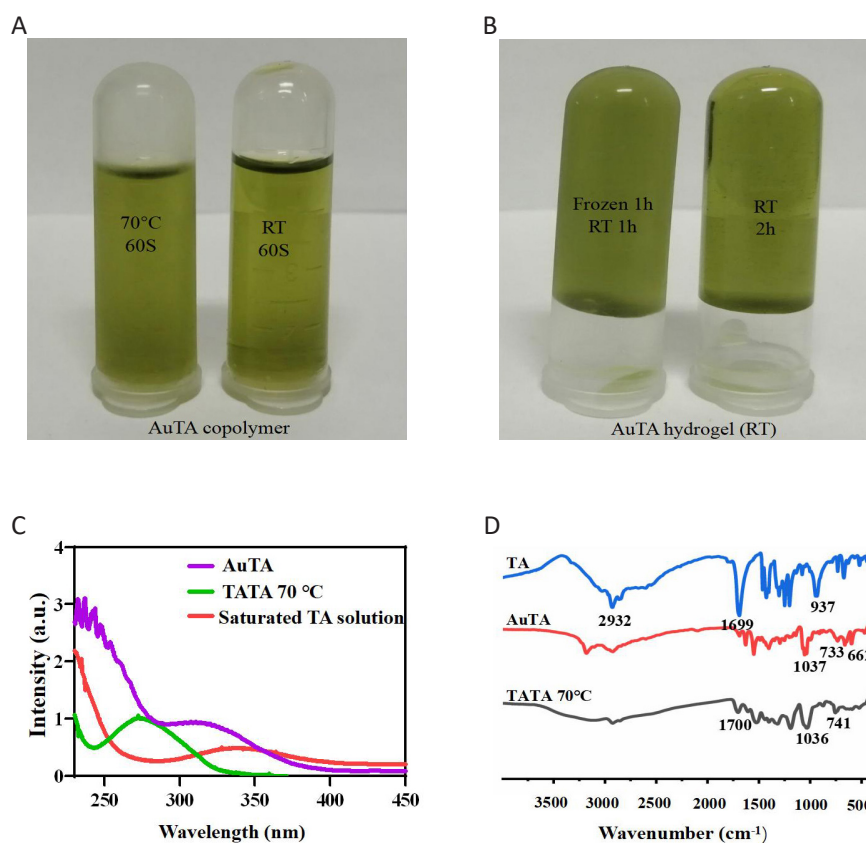


Figure 4. Photographs of AuTA copolymer and AuTA hydrogel were obtained at different temperatures. A: AuTA copolymer synthesized at 70°C (left) and RT (right); B: AuTA hydrogel synthesized at RT with different post-processing; C: UV-vis absorption spectra; D: FT-IR spectra of TA and the AuTA hydrogel (RT) and TATA hydrogel (70°C).

College Students of Weifang Medical University.

Conflicts of Interest

The authors declared no competing financial interest.

Author Contribution

Wang X was responsible for data curation and writing the original draft; Qin J was responsible for data curation; Lv Y was responsible for methodology and reviewing the manuscript; Ma J was responsible for conceptualization, methodology and editing the manuscript.

Abbreviation List

AuNSs, Gold nanostars

AuTA, Gold nanostars-thioctic acid

Poly (TA), Poly thioctic acid

ROP, Ring-opening polymerization

TATA, Tannic acid-thioctic acid

References

- [1] Raeisi M, Tsarevsky NV. Radical ring-opening polymerization of lipoates: Kinetic and thermodynamic aspects. *J Polym Sci*, 2021; 59: 675-684. DOI: 10.1002/pol.20200765.
- [2] Zhao L, Ren Z, Liu X et al. A multifunctional, self-healing, self-adhesive, and conductive sodium alginate/poly (vinyl alcohol) composite hydrogel as a flexible strain sensor. *ACS Appl Mater Inter*, 2021; 13: 11344-11355. DOI: 10.1021/acsami.1c01343.
- [3] Wang Y, Sun S, Wu P. Adaptive ionogel paint from room-temperature autonomous polymerization of α -thioctic acid for stretchable and healable electronics. *Adv Funct Mater*, 2021; 31: 2101494. DOI: 10.1002/adfm.202101494.
- [4] Cai C, Wu S, Tan Z et al. On-site supramolecular adhesion to wet and soft surfaces via solvent exchange. *ACS Appl Mater Inter*, 2021; 13: 53083-53090. DOI: 10.1021/acsami.1c15959.
- [5] Chen C, Yang X, Li S et al. Tannic acid-thioctic acid hydrogel: a novel injectable supramolecular adhesive gel for wound healing. *Green Chem*, 2021; 23: 1794-1804. DOI: 10.1039/d0gc02909b.
- [6] Zhang Q, Shi CY, Qu DH et al. Exploring a naturally tailored small molecule for stretchable, self-healing, and adhesive supramolecular polymers. *Sci Adv*, 2018; 4: eaat8192. DOI: 10.1126/sciadv.aat8192.
- [7] Deng Y, Zhang Q, Feringa BL et al. Toughening a self-healable supramolecular polymer by ionic cluster-enhanced iron-carboxylate complexes. *Angew Chem*, 2020; 132: 5316-5321. DOI: 10.1002/anie.201913893.
- [8] Dang C, Wang M, Yu J et al. Transparent, highly stretchable, rehealable, sensing, and fully recyclable ionic conductors fabricated by one-step polymerization based on a small biological molecule. *Adv Funct Mater*, 2019; 29: 1902467. DOI: 10.1002/adfm.201902467.
- [9] Zhang Q, Deng YX, Luo HX et al. Assembling a natural small molecule into a supramolecular network with high structural order and dynamic functions. *J Am Chem Soc*, 2019; 141: 12804-12814. DOI: 10.1021/jacs.9b05740.